**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/445, 31/395, 31/47
A61K 31/40, 31/55, 31/415
A61K 31/38

A1

(11) International Publication Number: WO 93/03725

(43) International Publication Date: 4 March 1993 (04.03.93)

(21) International Application Number: PCT/GB92/01519

(22) International Filing Date: 18 August 1992 (18.08.92)

(30) Priority data:

| | | |
|---|---|---|
| 9117943.2 | 20 August 1991 (20.08.91) | GB |
| 9119692.3 | 14 September 1991 (14.09.91) | GB |
| 9201414.1 | 23 January 1992 (23.01.92) | GB |
| 9203977.5 | 25 February 1992 (25.02.92) | GB |
| 9208321.1 | 15 April 1992 (15.04.92) | GB |

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KING, Francis, David [GB/GB]; GASTER, Laramie, Mary [GB/GB]; JOINER, Graham, Francis [GB/GB]; RAHMAN, Shirley, Katherine [GB/GB]; SANGER, Gareth, John [GB/GB]; WARDLE, Kay, Alison [GB/GB]; BAXTER, Gordon, Smith [GB/GB]; KENNETT, Guy, Anthony [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). YOUNG, Rodney, Christopher [GB/GB]; VIMAL, Mythily [LK/GB]; KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*



(54) Title: 5-HT4 RECEPTOR ANTAGONISTS

(57) Abstract

Compounds of formula (I): X-CO-Y-Z wherein the variable groups are as defined in the specification, of use in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | FI | Finland | MN | Mongolia |
| AU | Australia | FR | France | MR | Mauritania |
| BB | Barbados | GA | Gabon | MW | Malawi |
| BE | Belgium | GB | United Kingdom | NL | Netherlands |
| BF | Burkina Faso | GN | Guinea | NO | Norway |
| BG | Bulgaria | GR | Greece | NZ | New Zealand |
| BJ | Benin | HU | Hungary | PL | Poland |
| BR | Brazil | IE | Ireland | PT | Portugal |
| CA | Canada | IT | Italy | RO | Romania |
| CF | Central African Republic | JP | Japan | RU | Russian Federation |
| CG | Congo | KP | Democratic People's Republic of Korea | SD | Sudan |
| CH | Switzerland | | | SE | Sweden |
| CI | Côte d'Ivoire | KR | Republic of Korea | SK | Slovak Republic |
| CM | Cameroon | LI | Liechtenstein | SN | Senegal |
| CS | Czechoslovakia | LK | Sri Lanka | SU | Soviet Union |
| CZ | Czech Republic | LU | Luxembourg | TD | Chad |
| DE | Germany | MC | Monaco | TG | Togo |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |

# 5-HT4 RECEPTOR ANTAGONISTS

This invention relates to the use of compounds as 5-$HT_4$ receptor antagonists in the treatment of gastrointestinal disorders, CNS disorders and/or cardiovascular disorders, and to certain novel compounds having 5-$HT_4$ receptor antagonist activity.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-$HT_4$ receptor, and that ICS 205-930, which is also a 5-$HT_3$ receptor antagonist, acts as an antagonist at this receptor.

PCT/GB91/00650 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-$HT_4$ receptor antagonists in the treatment of atrial arrhythmias and stroke.

Some 5-$HT_3$ receptor antagonists have been disclosed as of potential use in the treatment of certain aspects of irritable bowel syndrome [see EP-A-189002 (Sandoz Limited) and EP-A-200444 (Beecham Group p.l.c)].

5-$HT_3$ receptor interactions which are of potential use in the treatment of IBS are those associated either with the visceral pain and abnormal perception of sensation aspects of this disease, or they are related to the ability of some 5-$HT_3$ receptor antagonists to cause constipation in volunteers.

Some 5-$HT_3$ receptor antagonists have been disclosed as of potential use in the treatment of gastrointestinal disorders associated with upper gut motility [see EP-A-226266 (Glaxo Group Ltd.) and EP-A-189002 (Sandoz Limited)]. 5-$HT_3$ receptor antagonists are also well known antiemetics, such as ondansetron, granisetron and tropisetron (see Drugs of the Future 1989, 14 (9) p.875 - F.D. King and G.J. Sanger).

EP-A-189002 (Sandoz Limited) and EP-A-429984 (Nisshin Flour Milling Co., Ltd.) disclose compounds which are described as 5-$HT_3$ receptor antagonists useful in the treatment of gastrointestinal disorders.

We have now discovered that certain of these compounds and related compounds act as antagonists at 5-$HT_4$ receptors and are of potential use in the treatment of IBS or atrial arrhythmias and stroke.

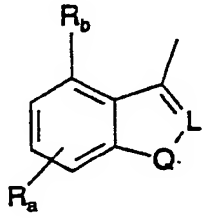
The compounds of the present invention also have a potential use in the treatment of CNS disorders such as anxiety and/or migraine, in the treatment of upper gut motility disorders and as antiemetics.

When used herein, 'treatment' includes prophylaxis as appropriate.

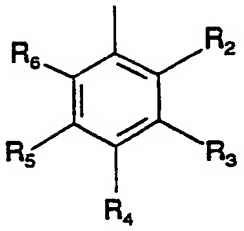
The invention therefore provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

X-CO-Y-Z (I)

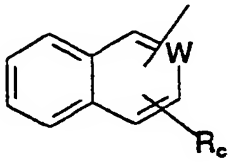
wherein
X is a group of formula (a), (b) or (c):




(a)




(b)




(c)

wherein

L is N or $CR_s$ wherein $R_s$ is hydrogen, $C_{1-6}$ alkoxy, halogen, $C_{1-4}$ alkyl or cyano;

Q is $NR_1$, $CH_2$, O or S;

W is CH or N;

$R_a$ is hydrogen, halo, $C_{1-6}$ alkyl, amino, nitro or $C_{1-6}$ alkoxy;

$R_b$ is hydrogen, halo, $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy;

$R_1$ is hydrogen, $C_{1-10}$ alkyl, $C_{2-6}$ alkenyl, aralkyl, $C_{2-6}$ alkanoyl or $C_{2-6}$ alkanoyl $C_{1-3}$ alkyl;

$R_2$ is $C_{1-6}$ alkoxy; and

$R_3$ is hydrogen, chloro or fluoro;

$R_4$ is hydrogen,$C_{1-6}$ alkyl, amino optionally substituted by a $C_{1-6}$ alkyl group, halo, hydroxy or $C_{1-6}$ alkoxy;

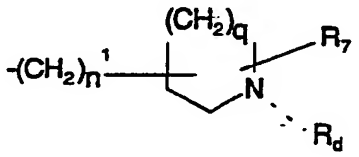
$R_5$ is hydrogen, halo, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, nitro, amino or $C_{1-6}$ alkylthio; and

$R_6$ is hydrogen, halo, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy or amino;

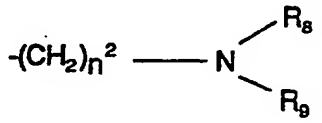
$R_c$ is hydrogen, $C_{1-6}$ alkoxy, halo or $C_{1-6}$ alkyl;

Y is O or NH;

Z is of sub-formula (d) or (e):




(d)




(e)

wherein

$n^1$ is 0, 1, 2, 3 or 4; $n^2$ is 2, 3, 4 or 5;

q is 0, 1, 2 or 3;

$R_d$ is hydrogen, $C_{1-12}$ alkyl or aralkyl;

$R_7$ and $R_8$ are hydrogen or $C_{1-6}$ alkyl; and

$R_9$ is hydrogen or $C_{1-10}$ alkyl;

in the manufacture of a medicament for use as a 5-$HT_4$ receptor antagonist.

Examples of alkyl or alkyl containing groups include $C_1$, $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_7$, $C_8$, $C_9$, $C_{10}$, $C_{11}$ or $C_{12}$ branched, straight chained or cyclic alkyl, as appropriate. $C_{1-4}$ alkyl groups include methyl, ethyl *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Alkenyl includes all suitable values including *E* and *Z* forms.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy.

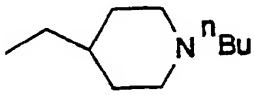
Halo includes fluoro, chloro, bromo and iodo.

When Z is of sub-formula (d), $n^1$ is preferably 2, 3 or 4 when the azacycle is attached at the nitrogen atom and $n^1$ is preferably 1 when the azacycle is attached at a carbon atom, such as the 4-position when q is 2.

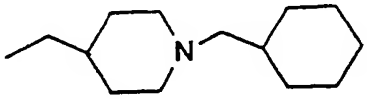
When Z is of sub-formula (e), $n^2$ is preferably 2, 3 or 4.

$R_8$ and $R_9$ are preferably both alkyl, especially one of $R_8$ and $R_9$ is $C_4$ or larger alkyl.

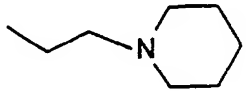
Specific values of Z of particular interest are as follows:



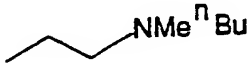
(i)



(ii)



(iii)



(iv)

The invention also provides novel compounds within formula (I) with side chains (i), (ii), (iii) or (iv).

The invention also provides novel compounds within formula (I) wherein X is of formula (a) wherein L is C-$OCH_3$, C-$CH_3$ or C- Cl, in particular those wherein the side chain Z is of sub-formula (i), (ii), (iii) or (iv).

Other values of Z of interest are described with reference to the Examples, such as those in Examples 19 onwards. In particular, the side chain of formula (i) or (ii) is replaced by a corresponding side chain with an alkyl or optionally substituted benzyl N-substituent and/or wherein the 4-piperidinyl group is replaced by 3-azetidinyl or 3-pyrrolidinyl.

L in formula (a) is favourably C-H, C-$CH_3$, C-Cl or C-$OCH_3$.

Q in formula (a) is favourably $NR_1$, usually NH or N-methyl.

$R_1$ is preferably hydrogen or a methyl or ethyl group.

$R_2$ is preferably methoxy.

$R_4$ is preferably amino.

$R_5$ is preferably halo.

$R_6$ is preferably hydrogen.

A substituent when halo is selected from fluoro, chloro, bromo and iodo, preferably chloro. $R_b$ when halo is preferably iodo.

Y is preferably O.

Particularly suitable examples of compounds of formula (I) include those described in the Examples hereinafter and in Example 2 of EP-A-429984.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds $R_x$-T wherein $R_x$ is $C_{1-6}$ alkyl, phenyl-$C_{1-6}$ alkyl or $C_{5-7}$ cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of $R_x$ include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

5-$HT_4$ receptor antagonist activity may be identified according to standard methods, such as those described hereinafter.

Examples of 5-$HT_4$ receptor antagonists include ICS 205-930 (tropisetron), which is described in the above mentioned patent references and GB 2125398A, R 50 595 (Janssen), which is described in FR76530 and Eur.J. Pharmacol., 181 119-125 (1990), and SDZ 205-557, which is described by K.H. Buchheit and R. Gamse in Naunyn-Schmiedeberg's Arch. Pharmacol., 343 (Suppl.), R101 (1991).

In one aspect, the compound of formula (I) is a more potent antagonist at 5-$HT_4$ receptors than at 5-$HT_3$ receptors.

Preferably, the 5-$HT_4$ receptor antagonist of formula (I) is in substantially pure pharmaceutically acceptable form.

The compounds of formula (I) may be prepared as described in the aforementioned patent references, or by analogous methods thereto.

The compounds of the present invention are 5-$HT_4$ receptor antagonists

and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-$HT_4$ receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and sytemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48

hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-$HT_4$ receptors, and hence that administration of a 5-$HT_4$ antagonist is of potential benefit in relieving a migraine attack.

The invention also provides a 5-$HT_4$ antagonist pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositries, injectable and infusable solutions or suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose,

carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds to be administered, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70 kg adult will normally contain 0.05 to 1000 mg for example 0.5 to 500 mg, of the compound. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50 mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions relate to the preparation of side chain (Z containing) intermediates.

## Examples

| | X | Y | Z |
|---|---|---|---|
| E1 | (a), L = CH, $R_a/R_b$ = H, Q = NH. | O | $CH_2$-(1-ethyl-4-piperidyl) |
| E2 | (b), $R_6$=H $R_2$ = OMe, $R_3$ = H, $R_4$ = $NH_2$, $R_5$ = Cl. | O | $(CH_2)_2$-(1-piperidyl) |
| E3 | (b), $R_6$=H $R_2$ = OMe, $R_3$ = F, $R_4$ = $NH_2$, $R_5$ = Cl. | NH | $CH_2$-(1-ethyl-4-piperidyl) |
| E4 | (b), $R_6$=H $R_2$ = OMe, $R_3$ = H, $R_4$ = $NH_2$, $R_5$ = Cl. | O | $CH_2$-(1-butyl-4-piperidyl) |
| E5 | (as E3) | O | $CH_2$-(1-butyl-4-piperidyl) |
| E6 | (as E1) | O | $CH_2$-(1-butyl-4-piperidyl) |

Examples (contd.)

| | X | Y | Z |
|---|---|---|---|
| E7 | (c),*<br>W = CH,<br>$R_c$ = 3-OMe | O | $CH_2$-(1-butyl-4-piperidyl) |
| E8 | (c),*<br>W = N | O | $CH_2$-(1-butyl-4-piperidyl) |
| E9 | (c),**<br>W = N | O | $CH_2$-(1-butyl-4-piperidyl) |
| E10 | (a),<br>L = N,<br>$R_a/R_b$ = H,<br>Q = NMe | O | $CH_2$-(1-butyl-4-piperidyl) |
| E11 | (as E1) | O | $(CH_2)_2$-(1-homopiperidyl) |
| E12 | (as E1) | O | $(CH_2)_3$-(1-piperidyl) |
| E13 | (as E1) | O | $(CH_2)_4$-(1-piperidyl) |
| E14 | (a),<br>L = CH,<br>$R_a$ = 5-Br,<br>$R_b$ = H<br>Q = NH | O | $(CH_2)_2$-(1-piperidyl) |

* 1-substituted

**3-substituted

Examples (contd.)

| | X | Y | Z |
|---|---|---|---|
| E15 | (b), $R_2$ = OMe, $R_3$ = H, $R_4$ = Me, $R_5$ = Cl | O | $(CH_2)_2$-(1-piperidyl) |
| E16 | (a), L = $COCH_3$, $R_a/R_b$ = H, Q = NH | O | $(CH_2)_2$-(1-piperidyl) |
| E17 | (a), L = CH, $R_a/R_b$ = H, Q = $CH_2$ | O | $(CH_2$-(1-butyl-4-piperidyl) |
| E18 | (a), L = CH, $R_a/R_b$ = H, Q = S | O | $(CH_2)_2$-(1-piperidyl) |
| E19 | (as E2) | O | $CH_2$-(1-butyl-3-pyrrolidinyl) |
| E20 | (as E1) | O | $CH_2$-(1-butyl-3-pyrrolidinyl) |
| E21 | (as E2) | O | $(CH_2)_2$-(1-pentyl-3-pyrrolidinyl) |
| E22 | (as E1) | O | $(CH_2)_2$-(1-pentyl-3-pyrrolidinyl) |
| E23 | (as E2) | O | $CH_2$-(hexahydro-1-butyl-3-azepinyl) |

Examples (contd.)

| | | X | Y | Z |
|---|---|---|---|---|
| | E24 | (as E1) | O | $CH_2$-(hexahydro-1-butyl-3-azepinyl) |
| | E25 | (as E2) | O | $(CH_2)_2$-(1-butyl-3-piperidyl) |
| | E26 | (as E1) | O | $(CH_2)_2$-(1-butyl-3-piperidyl) |
| | E27 | (as E2) | O | $(CH_2)_2$-(1-butyl-2-piperidyl) |
| | E28 | (as E2) | O | $CH_2$-(1-butyl-3-piperidyl) |
| | E29 | (as E1) | O | $CH_2$-(1-butyl-3-piperidyl) |
| | E30 | (as E2) | O | 1-butyl-4-piperidyl |
| | E31 | (as E2) | O | $CH_2$-(1-butyl-1,2,5,6-tetrahydropyridyl) |
| | E32 | (a), L = CH, $R_a/R_b$ = H, Q = NEt | O | (i) |
| | E33 | (a), L = CH, $R_a/R_b$ = H, Q = $NCH_3$ | O | (i) |
| | E34 | (as E33) | O | (ii) |
| | E35 | (as E2) | O | $CH_2$-(1-butyl-3-azetidinyl) |

**Examples** (contd.)

| | X | Y | Z |
|---|---|---|---|
| E36 | (a), L = C-$CH_3$ $R_a/R_b$ = H, Q = NH | O | $CH_2$-(1-butyl-4-piperidyl) |
| E37 | (a), L = C-Cl $R_a/R_b$ = H, Q = $NCH_3$ | O | $CH_2$-(1-butyl-4-piperidyl) |
| E38 | (a), L = C-$OCH_3$ $R_a/R_b$ = H, Q = NH | O | $CH_2$-(1-butyl-4-piperidyl) |
| E39 | (a), L = C-H $R_a/R_b$ = H, Q = NH | NH | $CH_2$-(1-butyl-4-piperidyl) |
| E40 | (a), $R_a/R_b$ = H Q = NH | NH | $CH_2$-(1-butyl-4-piperidyl) |
| E41 | (as E36) | O | ($CH_2$)-(1-piperidyl) |
| E42 | (b), $R_6$=H $R_2$=OMe, $R_3$=Cl, $R_4$=$NH_2$ $R_5$=Cl | O | (i) |

**Description 1** (intermediates for Examples 19 and 20)

a) **1-Butyl-3-carbomethoxypyrrolid-5-one**

To a cooled solution of butylamine (9.4 ml) in methanol (10 ml) was added, dropwise, dimethyl itaconate (15g). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to afford crude 1-butyl-3-carbomethoxy-pyrrolidin-5-one (17.9g).

b) **1-Butyl-3-hydroxymethylpyrrolidine**

To a stirred slurry of lithium aluminium hydride (4.29g) in diethyl ether (70 ml) was added 1-butyl-3-carbomethoxypyrrolid-5-one (10g) in diethyl ether (20 ml). The reaction mixture has maintained at reflux for 3h under a nitrogen atmosphere, and stirring continued overnight at room temperature. The mixture was cooled and water (4 ml), 10% aqueous NaOH (6 ml) and water (8 ml) were added sequentially. Diethyl ether was added and the mixture stirred for 1h. The resultant precipitate was removed by filtration through keiselguhr and the filtrate concentrated under reduced pressure. Distillation at reduced pressure gave pure 1-butyl-3-hydroxymethylpyrrolidine (D1) (5.13g).

$^1H$ NMR ($CDCl_3$) 250 MHz δ: 3.69 (dd, 1H), 3.51 (dd, 1H), 2.80 (dt, 1H), 2.64 (dd, 1H), 2.24-2.53 (m, 5H), 1.92-2.07 (m, 1H), 1.60-1.73 (m, 1H), 1.26-1.55 (m, 4H), 0.92 (t, 3H).

**Description 2** (intermediate for Examples 21 and 22)

a) Following the procedures outlined in Description 1, the following compound was obtained:

1-pentyl-3-hydroxymethylpyrrolidine

b) 3-Chloromethyl-1-pentylpyrrolidine (6.54g) in chloroform (10 ml) was saturated with hydrogen chloride and the mixture heated to reflux. A solution of thionyl chloride (5.6 ml) in chloroform (10 ml) was added dropwise and stirring continued for 1h. The reaction mixture was cooled

to room temperature and stirring continued overnight. The reaction mixture was concentrated to half-volume and azeotroped with ethanol (2 x 10 ml). The residue was diluted with water and extracted with diethyl ether. The aqueous phase was basified with 50% aqueous sodium hydroxide and extracted with diethyl ether. The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo* to afford an oil. Distillation under reduced pressure gave pure 3-chloromethyl-1-pentylpyrrolidine (5.79g).

A stirred solution of 3-chloromethyl-1-pentyl pyrrolidine (5.415g), tricaprylmethyl ammonium chloride (375 mg), and sodium cyanide (7.25g) in water (12.5 ml) was heated at 100°C for 24h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo* to afford crude 3-cyanomethyl-1-pentylpyrrolidine (5.04g).

d) A solution of 3-cyanomethyl-1-pentylpyrrolidine (2.982g) in methanolic HCl (60 ml) was allowed to stand at room temperature for 16h. The solvent was removed under reduced pressure, the residue diluted with water, basified with aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with water, dried ($Na_2SO_4$) filtered and concentrated *in vacuo* to afford crude methyl 3-(1-pentyl pyrrolidino) acetate. Distillation under reduced pressure (100°C at 0.2 mm Hg) gave title compound (2.13g).

e) To a suspension of lithium aluminium hydride (0.7g) in diethyl ether (40 ml) was added methyl 3-(1-pentyl pyrrolidino) acetate (1.967g) under a nitrogen atmosphere. The mixture was heated to reflux and stirring continued for 4h. The reaction mixture was cooled to room temperature and stirring continued overnight. Water (5 ml) was added dropwise and the resultant precipitate removed by filtration and washed with dichloromethane. The combined organic filtrate was concentrated *in vacuo* to afford an oil. Distillation under reduced pressure (150°C / 1.0 mm Hg) gave pure 3-hydroxyethyl-1-pentylpyrrolidine (D2) (1.48g).

$^1H$ NMR (250 MHz) ($CDCl_3$) δ: 4.18-4.41 (s, 1H), 3.52-3.73 (m, 2H), 2.76-2.85 (m, 1H), 2.33-2.52 (m, 6H), 1.92-2.08 (m, 1H), 1.45-1.80 (m, 5H), 1.22-1.38 (m, 4H), 0.88 (t, 3H).

**Description 3** (intermediate for Examples 23 and 24)

a) **Hexahydro-1-butyl-azepin-2-one**

To a solution of hexahydro-1H-azepin-2-one (10g) in dry THF (300 ml) was added potassium tert-butoxide (9.86g). The reaction mixture was heated to reflux. 1-Bromobutane (9.45 ml) was added after 1h. Stirring was continued for 2h. The reaction mixture was cooled to room temperature and water (10 ml) added. The solvent was concentrated under reduced pressure and the residue dissolved in ethyl acetate (250 ml) and washed with brine. The organic phase was dried ($Na_2SO_4$) filtered and concentrated *in vacuo* to afford an oil.

Kugelröhr distillation afforded pure title compound (12.0g).

b) **Hexahydro-1-butyl-3-carboxyazepin-2-one**

To a solution of hexahydro-1-butylazepin-2-one (6.0g) in dry THF (30 ml) was added lithium diisopropylamide in cyclohexane (1.5M, 23.3 ml) at 0°C. Stirring was continued at ambient temperature for 30 min. $CO_2$ pellets was added to the reaction mixture which were subsequently poured into ice-water (200 ml). The THF was concentrated *in vacuo* and the aqueous phase adjusted to pH2 with 5N HCl. The aqueous phase was extracted with chloroform (4 x 200 ml) and the combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to afford an oil. Flash chromatography on silica using chloroform and ethanol as the eluant gave pure title compound (1.90g).

c) **Hexahydro-1-butyl-3-hydroxymethylazepine**

To a slurry of lithium aluminium hydride (1.03g) in THF (50 ml) was added a solution of hexahydro-1-butyl 3-carboxyl azepin-2-one (1.90g) in THF (50 ml) under a nitrogen atmosphere. Stirring was continued at ambient temperature for 70h. The reaction mixture was heated to reflux for 5h, cooled and quenched by the sequential addition of water (1 ml), 10% aqueous NaOH (1½ ml) and water (2½ ml). Stirring was continued at room temperature for 1h. The resultant precipitate was removed by filtration and the filtrate concentrated *in vacuo* to afford an oil.

Kughlerohr distillation gave pure title compound (D3) (0.76g).

$^1$H NMR ($CDCl_3$) 250 MHz δ: 4.71 (m, 1H), 3.81 (dd, 1H), 3.49-3.57 (m, 1H), 2.70-2.85 (m, 3H), 2.43 (dt, 2H), 2.07-2.30 (m, 1H), 1.41-1.90 (m, 9H), 1.22-1.37 (m, 2H), 0.92 (t, 3H).

**Description 4** (intermediate for Examples 25 and 26)

a) **Ethyl 1-butyl-3-pyridylacetate iodide**

To a cooled solution of ethyl 3-pyridylacetate (12g) in acetone (50 ml) was added 1-iodobutane (12.90 ml). The reaction mixture was stirred at room temperature overnight and then heated to reflux. The reaction mixture was cooled to room temperature and diethyl ether was added. Stirring was continued for 15 min. The resultant precipitate was removed by filtration and dried to afford crude title compound (23.76g).

b) **Ethyl-1-butyl-3-piperidylacetate**

A solution of ethyl 1-butyl-3-pyridylacetate iodide (21g) in ethanol was hydrogenated over $PtO_2$ (2g) at atmospheric pressure and room temperature. The catalyst was removed by filtration through keiselguhr and the filtrate concentrated *in vacuo*. The residue was dissolved in water, basified from $K_2CO_3$ and extracted with chloroform. The organic phase was dried ($Na_2SO_4$) filtered and concentrated *in vacuo* to afford ethyl 1-butyl-3-piperidylacetate (13.6g) as an oil.

c) **1-Butyl-3-piperidylethanol**

To a slurry of lithium aluminium hydride (3.51g) in diethyl ether (50 ml) was added, dropwise, a solution of ethyl 1-butyl-3-piperidyl acetate (7.0g) in diethyl ether (50 ml) at 0°C under a nitrogen atmosphere. Stirring was continued at ambient temperature for 60h. The reaction mixture was cooled to 0°C and treated sequentially with water (3.5 ml), 10% aqueous NaOH (5.2 ml) and water (8.7 ml). Stirring was continued for 1h. The precipitate was removed by filtration through Keiselguhr and the filtrate evaporated under reduced pressure to afford crude product. Vacuum

distillation gave pure title compound (D4) (4.0g).

$^1$H NMR ($CDCl_3$) 250 MHz δ: 3.59-3.77 (m, 2H), 2.64-2.69 (m, 2H), 2.23-2.35 (m, 2H), 2.11-1.96 (m, 1H), 1.40-1.88 (m, 9H), 1.22-1.38 (m, 2H), 0.98-1.14 (m, 1H), 0.92 (t, 3H).

$MH^+$ 186

**Description 5** (intermediate for Example 27)

a) **Ethyl 1-butyl-2-piperidylacetate**

To a solution of ethyl 1H-piperidyl-2-acetate (8.3g) in ethanol (100 ml) was added potassium carbonate (14.35g) and 1-bromo butane (11.7 ml). The reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered through keiselguhr. The filtrate was evaporated under reduced pressure to afford an oil. Flash chromatography on silica eluting with chloroform and ethanol gave pure title compound (5.85g).

b) **1-Butyl-2-piperidylethanol**

Following the procedure outlined in Description 4c), ethyl 1-butyl-2-piperidyl acetate (4.44g) gave the title compound as an oil after kugelrohr distillation (2.27g).

$^1$H NMR ($CDCl_3$) 250 MHz δ: 5.45 (m, 1H), 3.82-3.94 (m, 1H), 3.70-3.80 (m, 1H), 3.00-3.09 (m, 1H), 2.73-2.85 (m, 1H), 2.61-2.72 (m, 1H), 2.40-2.52 (m, 1H), 2.21-2.34 (m, 1H), 1.81-1.96 (m, 1H), 1.23-1.75 (m, 11H), 0.90 (t, 3H).

$MH^+$ 186

**Description 6** (intermediate for Example 28)

a) **Ethyl-1-butyl-3-piperidyl carboxylate**

Following the procedure outlined in description 5a), ethyl-1H-piperidyl 3-carboxylate (15.7g) gave title compound (17.1g).

b) **1-Butyl-3-piperidylmethanol**

Following the procedure outlined in Description 5b), ethyl 1-butyl -3-piperidyl carboxylate (17.1g) gave 1-butyl 3-piperidinyl methanol (D6) (3.9g).

$^1$H NMR (250 MHz) ($CDCl_3$) δ: 3.38-3.53 (m, 2H), 2.82-3.03 (m, 2H), 2.23-2.34 (m, 2H), 1.98-2.02 (m, 1H), 1.36-1.97 (m, 8H), 1.22-1.35 (m, 2H), 0.92 (t, 3H).

**Description 7** (intermediate for Example 30)

a) **Dimethyl-2, 2'-butyliminodiethanoate**

Methyl acrylate (11.78g) was added dropwise to n-butylamine (5g), at 0°C. The reaction mixture was heated to reflux for 24h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water (3x). The organic phase was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford an oil. Purification by kugelrohr distillation gave the title compound (9.95g).

b) **1-Butyl-4-piperidone**

Potassium *tert*-butoxide (6.82g) was added to a solution of dimethyl-2,2'-butyl iminodiethanoate (9.95g) in diethyl ether under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. The mixture was extracted into 5N HCl (100 ml) and heated under reflux for 2h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was basified with $K_2CO_3$ and extracted with ethyl acetate. The organic phase was dried

($Na_2SO_4$) filtered and concentrated *in vacuo*. Flash chromatography on silica using ethyl acetate as the eluant gave pure 1-butyl-4-piperidone (3.68g).

c) **1-Butyl-4-piperidol**

To a slurry of lithium aluminium hydride (0.96g) in diethyl ether (50 ml) was added 1-butyl-4-piperidinone (2.6g) in diethyl ether (50 ml), at 0°C under a nitrogen atmosphere. The reaction mixture was stirred overnight at ambient temperature, cooled to 0°C and treated sequentially with water (1.0 ml), 10% NaOH (1.4 ml) and water (2.4 ml). The mixture was stirred at ambient temperature for 1h and the precipitate removed by filtration through keiselguhr. The filtrate was concentrated under reduced pressure to afford an oil. Purification by vacuum distillation gave 1-butyl-4-piperidol (D7) (1.98g).

$^1H$ NMR ($CDCl_3$) 250 MHz δ: 3.61-3.74 (m,1 H), 2.71-2.82 (m, 2H), 2.26-2.34 (m, 2H), 2.04-2.16 (m, 2H), 1.82-1.95 (m, 3H), 1.38-1.67 (m, 4H), 1.22-1.37 (m, 2H), 0.9 (t, 3H).

**Description 8** (intermediate for Example 31)

a) **Ethyl 1-butyl-4-pyridyl carboxylate iodide**

Following the procedure outlined in Description 4a), ethyl 4-pyridine carboxylate (10g) gave the title compound (22.2g).

b) **Ethyl 2-butyl-(1,2,5,6)-tetrahydropiperidyl-4-carboxylate**

To a suspension of sodium borohydride (4.6g) in ethanol (300 ml), at 0°C, was added ethyl 1-butyl-4-pyridyl carboxylate iodide (10g) under an atmosphere of nitrogen. The reaction mixture was stirred for 2h at ambient temperautre. The mixture was poured into water and the solvent concentrated under reduced pressure. The residue was extracted into chloroform and the organic phase dried ($Na_2SO_4$), filtered and concentrated to afford an oil. Flash chromatography on silica using chloroform and ethanol as eluant gave pure title compound (2.59g).

c) **1-Butyl-(1,2,5,6)-tetrahydropiperidyl-4-methanol**

Following the procedure outlined in Description 4c), ethyl 1-butyl-(1,2,5,6)- tetrahydropiperidyl-4-carboxylate (2g) gave pure title compound (D8) (630 mg).

$^1$H NMR ($CDCl_3$) 250 MHz δ: 5.59 (s, 1H), 3.92 (s, 2H), 2.95 (s, 2H), 2.59 (t,2H), 2.35 -2.50 (m, 2H), 2.10-2.20 (m, 2H), 1.25-1.60 (m, 6H), 0.92 (t, 3H).

$M^+$ 169

**Description 9** (intermediate for Example 35)

a) **1-Benzyl-4-chloro-3-hydroxybutylamine**

To a solution of epichlorohydrin (150ml) in cyclohexane (1l) was added benzylamine (240ml). The reaction mixture was stirred at room temperature for 24h. The precipitate was removed by filtration, washed with petrol (bp 60-80°C) and dried (327.7g)

b) **1-Benzyl-3-trimethylsiloxyazetidine**

To a solution of imidazole (112g) and triethyl amine (825ml) in acetonitrile (1.5l) was added, dropwise chlorotrimethylsilane (203ml) at -5°C under nitrogen. Stirring was continued at room temperature for $1^1/_2$h. 1-benzyl-4-chloro-3-hydroxybutylamine (310g) was added to the reaction and the resulting mixture heated to reflux for 72h, with vigorous stirring. The mixture was cooled to room temperature, toluene (2l) was added and the mixture left to stand overnight. The precipitate was removed by filtration, slurried in petrol (bp 60-80°C) (2l) and washed with water (200ml). The filtrate was concentrated *in vacuo* and the residue partitioned between water and petrol (bp 60-80°C) (1l). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an oil. Purification by vacuum distillation gave 1-benzyl-3-trimethylsiloxy azetidine (130g) as a colourless oil.

c) **1-Benzyl-3-hydroxyazetidine**

A solution of 1-benzyl-3-trimethylsiloxyazetidine (89g) in cHCl/water (53/350ml) was stirred vigorously at room temperature for 10min. The mixture was basified with $K_2CO_3$ and extracted with diethyl ether. The ethereal extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1-benzyl-3-hydroxyazetidine (59.6g) as a white solid.

d) **1-Benzyl-3-cyanoazetidine**

To a stirred solution of 1-benzyl-3-hydroxyazetidine (83.1g) and triethylamine (71ml) in toluene (610ml) and triethylamine (71ml) was added, dropwise, over 20min methane sulphonyl chloride (39.5ml). During addition the internal temperature was maintained between 0 and 5°C. On completion of addition stirring was continued for a further 30min. Water (20ml) was added to the reaction mixture and the separated toluene layer removed. The aqueous layer was further extracted with toluene (2x100ml). The organic extracts were combined and washed with brine. The organic phase was treated with Adogen 464 (25g) and a solution of sodium cyanide (29.5g) in water (173ml). The reaction mixture was heated to reflux for $1\frac{1}{2}$h and allowed to cool to room temperature. The mixture was transferred to a separatory funnel and the aqueous layer removed. The organic phase was washed with water (3x200ml) and brine (200ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Distillation of the residue gave pure 1-benzyl-3-cyanoazetidine (62.9g).

e) **Methyl 1-benzyl-3-azetidinyl carboxylate**

To a solution of 1-benzyl-3-cyanoazetidine (10g) in methanol (40ml) was added $cH_2SO_4$ (35ml), dropwise, so as to maintain the reaction at a maximum 55°C. The reaction mixture was heated to 80°C for 2h, cooled to r.t. and poured into ice (240g). The mixture was basified with aq. ammonia and extracted into dichloromethane. The organic phase was washed with water, dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to afford crude title compound (10.18g).

f) **Methyl-1H-3-azetidinyl carboxylate acetate**

A solution of methyl 1-benzyl-3-azetidinyl carboxylate (5.45g) in ethanol (100ml) and acetic acid (6ml) was hydrogenated over 10% Pd/C at 50psi and 50°C for 6h. The catalyst was removed by filtration through keiselguhr and the filtrate concentrated *in vacuo* to afford methyl 1-H-3-azetidinyl carboxylate acetate (3.65g).

g) **Methyl 1-butyryl-3-azetidinyl carboxylate**

To a solution of methyl 1-H-3-azetidinyl carboxylate acetate (2.80g) and triethylamine (4.6ml) in dichloromethane (60ml) was added, dropwise, butyryl chloride (1.6ml). The reaction mixture was stirred at ambient temperature for 70h. The mixture was washed with water and the organic phase dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford crude methyl 1-butyryl-3-azetidinyl carboxylate (2.60g).

h) **1-Butyl-3-hydroxymethylazetidine**

To a solution of Lithium aluminium hydride (2.20g) in dry THF (25ml) was added a solution of methyl 1-butyryl-3-azetidinyl carboxylate (3.60g) in dry THF, at 0°C, under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched by sequential addition of water ($2^1/_2$ml), 10% aq. NaOH (4ml) and water (5ml). Diethyl ether (20ml) was added and stirring continued for 1h. The precipitate was removed by filtration through Keiselguhr and the filtrate concentrated *in vacuo* to afford an oil. Kughlerohr distillation afforded pure title compound (D9) (1.1g).

$^1H$ NMR 250MHz ($CDCl_3$), δ: 3.67 (d,2H), 3.23-3.47 (m,2H), 2.97-3.08 (m,2H), 2.55-2.68 (m,1H), 2.35-2.7 (m,2H), 1.27-1.38 (m,4H), 0.86-0.98 (m,3H), $MH^+$ 144

**Description 10** (intermediate for Example 4)

**1-Butyl-4-piperidinemethanol**

A mixture of ethyl isonipecotate (31.4g, 0.2mole), $K_2CO_3$ (54g, 0.4mole) and $^nBuBr$ (27.4g, 0.2mole) in EtOH (400ml) was stirred under reflux for 3 hours. The reaction mixture was allowed to cool, filtered through keiselguhr and the filtrate concentrated to give a pale yellow oil. This was dissolved in dry $Et_2O$ (200ml) and added dropwise to a suspension of $LiAlH_4$ (20g, 0.26mole) in dry $Et_2O$. The reaction mixture was stirred at room temperature overnight then cooled in an ice bath. Water (20ml) was carefully added, followed by 20% aq. NaOH (20ml), followed by water (60ml). The mixture was stirred at room temperature for 30 minutes then filtered through keiselguhr. The filtrate was concentrated *in vacuo* to give a colourless oil (25.0g).

$^1$NMR 250MHz ($CDCl_3$)

δ: 3.48(d,2H), 2.93-2.99(bd,2H), 1.18-2.4(m,14H), 0.9(t,3H)

**Preparation of Intermediate Acid for Example 3**

a) Methyl-4-acetamido-5-chloro-2-methoxybenzoate (10.9g) was dissolved in chloroform (40 ml), cooled to -10 C under nitrogen. A three molar excess of trifluoromethyl hypofluorite was slowly bubbled through the stirred, cooled solution for 6 hours. A slow positive nitrogen stream was maintained throughout the reaction. After warming to room temperature and thoroughly purging with nitrogen, the chloroform was removed *in vacuo*.

The residue was chromatographed on silica using chloroform with increasing amounts of methanol as eluant. Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate was isolated as an off white solid.

$^1$H NMR ($CDCl_3$) 250MHz; δ: 7.64 (d, 1H), 7.37 (bs, 1H), 3.98 (bs, 3H), 3.9 (s, 3H), 2.2 (s, 3H)

b) Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate (1.89g) in 25 ml ethanol was treated with a solution of sodium hydroxide (1.15g) in 15 ml water. The mixture was heated under reflux for 16 hours then cooled. The solvent was removed in vacuo and the residue acidified. The precipitated solid was collected by filtration to give 1.48g of 4-amino-5-chloro-3-fluoro-2-methoxybenzoic acid.

$^1$H NMR (DMSO) 250MHz; δ: 7.49 (d, 1H), 6.19 (bs, 2H), 3.80 (s, 3H)

**Example 1**

**(1-Ethyl-4-piperidyl)methyl-1H-indole-3-carboxylate (E1)**

A suspension of indole-3-carboxylic acid (500 mg, 0.003 mole) in dichloromethane (50 ml) was treated with oxalyl chloride (0.635, 0.005 mole) and two drops of dimethylformamide. The mixture was stirred at room temperature for one and a half hours then the solvent was removed *in vacuo*. The residue was redissolved in dichloromethane (50 ml) and a solution of triethylamine (612 mg, 0.006 mole) and 1-ethyl-4-hydroxymethylpiperidine (430 mg, 0.003 mole) in dichloromethane (20 ml) was added dropwise. The reaction mixture was stirred at room temperature overnight then washed with aqueous potassium carbonate solution and water, dried and concentrated to give a gummy solid which was purified by column chromatography on silica gel using chloroform 95%, methanol 5% as eluant to give a white solid 405 mg, mp 135-6°C.

$^1$H NMR (250MHz) $CDCl_3$; δ: 10.08 (bs, 1H), 8.10 - 8.20 (m, 1H), 7.76 (d, 1H), 7.35 - 7.45 (m, 1H), 7.20 - 7.28 (m, 2H), 4.20 (d, 2H), 3.0-3.12 (bd, 2H), 2.5 (dd, 2H), 1.4-2.10 (m, 7H), 1.10 (t, 3H).

**Example 2**

**4-Amino-5-chloro-2-methoxy-(2-(1-piperidyl)ethyl)benzoate (E2)**

A solution of 4-amino-3-chloro-2-methoxybenzoic acid (2.01g, 0.01 mole) in acetonitrile (30 ml) was treated with bis-carbonyldiimidazole (1.62g, 0.01 mole) and the mixture was stirred at room temperature for one and a half hours. The solvent was removed *in vacuo* to leave the crude imidazolide.

A solution of 1-(2-hydroxyethyl)piperidine (1.29g, 0,01 mole) in dry THF (10 ml) under an atmosphere of nitrogen, was cooled in an ice bath. n-Butyllithium (6.25 ml of 1.6M solution in hexane) was added dropwise and the resulting solution stirred at 0°C for 15 minutes.

The imidazolide was dissolved in dry THF (20 ml) and the resulting solution added dropwise to the solution of the lithium alkoxide at 0°C.

The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The chloroform was separated, washed several times with water, dried and concentrated to give a white solid (recrystallised from ether/petroleum ether) yield 2.6g, mp 135-6°C.

$^1$H NMR (250MHz) $CDCl_3$; δ: 7.82 (s, 1H), 6.30 (s, 1H), 4.48 (bs, 2H), 4.38 (t, 2H), 3.82 (s, 3H), 2.72 (t, 2H), 2.45-2.55 (m, 4H), 1.52-1.66 (m, 4H), 1.40-1.50 (m, 2H).

**Example 3**

**4-Amino-5-chloro-3-fluoro-2-methoxy-(1-ethyl-4-piperidyl)methylbenzamide** (E3)

A solution of 4-amino-5-chloro-3-fluoro-2-methoxybenzoic acid (210mg, 0.001 mole) in acetonitrile (15ml) was treated with bis-carbonyldiimidazole (162mg, 0.001 mole). The mixture was stirred at room temperature for one and a half hours.

A solution of 1-ethyl-4-aminomethylpiperidine (142 mg, 0.001 mole) in acetonitrile (10 ml) was added dropwise and the reaction mixture was stirred at room temperature for 3 hours.

The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The chloroform layer was removed, washed several times with water, dried and concentrated to give a beige solid which was converted to the hydrochloride salt, 110 mg, mp 208-9°C.

$^1$H NMR (250 MHz) $CDCl_3$ (free base); δ: 7.82 (d, 1H), 7.65-7.75 (bt, 1H), 4.30 (bs, 2H), 4.40 (s, 3H), 3.25 (t, 2H), 2.82-2.95 (bd, 2H), 2.28-2.38 (dd, 2H), 1.10-1.90 (m, 7H), 1.0 (t, 3H).

**Example 4**

**4-Amino-5-chloro-2-methoxy-(1-butyl-4-piperidyl)methyl benzoate (E4)**

The title compound was prepared from 4-amino-5-chloro-2-methoxybenzoic acid and 1-butyl-4-piperidinemethanol by the method described for Example 2. It was isolated as a white solid, mp 52-53°C.

$^1$H NMR (250 MHz) $CDCl_3$; δ: 7.80 (s, 1H), 6.28 (s, 1H), 4.42 (bs, 2H), 4.10 (d, 2H), 3.85 (s, 3H), 2.92-3.02 (bd, 2H), 2.35 (m, 2H), 1.20-2.02 (m, 11H), 0.92 (t, 3H).

**Example 5**

**4-Amino-5-chloro-3-fluoro-2-methoxy-(1-butyl-4-piperidyl)methyl benzoate (E5)**

The title compound was prepared from 4-amino-5-chloro-3-fluoro-2-methoxybenzoic acid and 1-butyl-4-piperidinemethanol by the method described for Example 2. It was isolated as a colourless gum and converted to the hydrochloride salt, mp 195-7°C.

$^1$H NMR (250 MHz) $CDCl_3$ (free base); δ: 7.62 (d, 1H), 4.45 (bs, 2H), 4.12 (d, 2H), 3.90 (s, 3H), 2.92-3.15 (bd, 2H), 2.28-2.38 (m, 2H), 1.20-2.00 (m, 11H), 0.90 (t, 3H).

**Example 6**

**(1-Butyl-4-piperidyl)methyl-1H-indole-3-carboxylate (E6)**

A suspension of indole-3-carboxylic acid (500mg, 0.003 mole) in dichloromethane (50 ml) was treated with oxalyl chloride (0.635g, 0.005 mole) and two drops of dimethylformamide. The mixture was stirred at room temperature for one and a half hours then the solvent was removed *in vacuo* to leave the acid chloride.

A solution of 1-butyl-4-piperidinemethanol (513 mg, 0.003 mole) in dry THF (10 ml) under an atmosphere of nitrogen, was cooled in an ice bath. n-Butyllithium (1.88 ml of 1.6m solution in hexane) was added dropwise and the resulting solution stirred at 0°C for 15 minutes.

The acid chloride was dissolved in dry THF (20 ml) and the solution added dropwise to the solution of the lithium alkoxide at 0°C.

The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The chloroform was separated, washed several times with water, dried and concentrated to give a pale brown gum.

$^1$H NMR (250 MHz) $CDCl_3$; δ: 9.90 (bs, 1H), 8.10-8.18 (m, 1H), 7.78 (d, 1H), 7.37-7.46 (m, 1H), 7.16-7.28 (m, 2H), 4.19 (d, 2H), 3.05-3.15 (bd, 2H), 2.40-2.49 (m, 2H), 1.20-2.18 (m, 11H), 0.90(t, 3H).

**Example 7**

**3-Methoxy-2-(1-butyl-4-piperidyl)methylnaphthoate (E7)**

The title compound was prepared from 3-methoxy-2-naphthoic acid and 1-butyl-4-piperidinemethanol by the method described for Example 2. It was isolated as a pink solid MP 65-6°C.

$^1$H NMR (250 MHz) $CDCl_3$; δ: 8.28 (s, 1H), 7.84 (d, 1H), 7.75 (d, 1H), 7.51 (t, 1H), 7.37 (t, 1H), 7.19 (s, 1H), 4.22 (d, 2H), 3.98 (s, 3H), 3.00 (bd, 2H), 2.32-2.40 (m, 2H), 1.24-2.03 (m, 11H), 0.92 (t, 3H).

**Example 8**

**(1-Butyl-4-piperidyl)methyl-isoquinoline-1-carboxylate (E8)**

The title compound was prepared from isoquinoline-1-carboxylic acid and 1-butyl-4-piperidine-methanol by the method described for Example 2. It was isolated as a colourless gum.

$^1$H NMR (250 MHz) $CDCl_3$; δ: 8.70 (dd, 1H), 8.65 (d, 1H), 7.88 (dd, 1H), 7.81 (d, 1H), 7.60-7.78 (m, 2H), 4.39 (d, 2H), 3.00 (bd, 2H), 2.28-2.39 (m, 2H), 1.20-2.05 (m, 11H), 0.90 (t, 3H).

**Example 9**

**(1-Butyl-4-piperidyl)methyl-isoquinoline-3-carboxylate (E9)**

The title compound was prepared from isoquinoline-3-carboxylic acid and 1-butyl-4-piperidinemethanol by the method described for Example 2. It was isolated as a white solid, mp 82-3°C.

$^1$HNMR (250 MHz) $CDCl_3$; δ: 9.38 (s, 1H), 8.60 (s, 1H), 8.10 (dd, 1H), 7.98 (dd, 1H), 7.70-7.87 (m, 2H), 4.35 (d, 2H), 3.00 (bd, 2H), 2.26-2.40 (m, 2H), 1.20-2.05 (m, 11H), 0.91 (t, 3H).

**Example 10**

**(1-Butyl-4-piperidyl)methyl-1-methylindazole-3-carboxylate (E10)**

The title compound was prepared in a similar manner to the compound of Example 6, from the 1-methylindazole acid (EP-A-323105)

m.p. 190°C. (hydrochloride salt).

**Reference: [1]U.K. Patent 1571278 (Soc. D'Etudes Sci. et. Ind. D'Ille de Fr.)**

**Examples 11 to 14**

The following compounds were prepared (as hydrochloride salts), in a similar manner to that described in EP-A-429984.

**(1-Homopiperidyl)ethyl-1H-indole-3-carboxylate (E11)**

m.p. 123-125°C

**(1-Piperidyl)propyl-1H-indole-3-carboxylate (E12)**

m.p. 184-187°C

**(1-Piperidyl)butyl-1H-indole-3-carboxylate (E13)**

m.p. 170-173°C

**(1-Piperidyl)ethyl-5-bromo-1H-indole-3-carboxylate (E14)**

m.p. 186-188°C

**Example 15**

**5-Chloro-2-methoxy-4-methyl-(2-(1-piperidyl)ethyl)benzoate (E15)**

The title compound was prepared in a similar manner to the compound of example 2, from 5-chloro-2-methoxy-4-methylbenzoic acid (J. Chem. Soc., 1963, p.730), and isolated as the hydrochloride salt, m.p. 185-186°C.

**Example 16**

**(1-Piperidylethyl)-2-methoxyindole-3-carboxylate hydrochloride (E16)**

Following the procedure outlined in GB 2125398A, Example A-5, (N-piperidylethyl)indole-3-carboxylate (0.21g) was converted to the title

compound (38mg, 16%).

$^1$H NMR ($CDCl_3$) 250MHz (free base)

δ: 9.25(brs,1H), 8.0(d,1H), 7.29(d,1H), 7.25-7.05(m,2H), 4.55(t,2H), 4.12(s,3H), 2.90(t,2H), 2.67(brs,4H), 1.75-1.6(m,4H), 1.55-1.35(m,2H).

**Example 17**

**(1-Butyl-4-piperidyl)methylindene-1-carboxylate hydrochloride (E17)**

A solution of indene-1-carboxylic acid (187mg) (N.H. Cromwell and D.B. Capps, J. Amer. Chem. Soc., 74, 44448, 1952) in dichloromethane (10ml) was treated with oxalyl chloride (100mg) and two drops of dimethylformamide. The mixture was stirred at room temperature for one and a half hours then the solvent was removed *in vacuo* to leave the acid chloride.

A solution of l-butyl-4-piperidinemethanol (120mg) in dry THF (5ml) under an atmosphere of nitrogen, was cooled in an ice bath. n-Butyllithium (0.5ml of 1.6m solution in hexane) was added dropwise and the resulting solution stirred at 0°c for 15 minutes.

The acid chloride was dissolved in dry THF (10ml) and the solution added dropwise to the solution of the lithium alkoxide at 0°C.

The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The chloroform was separated, washed several times with water, dried and concentrated to give a pale gum which was converted to the hydrochloride salt 120mg, mp 131-3°C.

$^1$H NMR (250MHz) $CDCl_3$

δ: 8.02(d,1H), 7.55-7.45(m,2H), 7.38(t,1H), 7.28(t,1H), 4.21(d,2H), 3.55(d,2H), 3.20(brd,2H), 2.65-1.25(m,13H), 0.95(t,3H).

**Example 18**

**2-(1-Piperidyl)ethyl-3-benzothiophene carboxylate** (E18)

Benzothiophene-3-carboxylic acid (J. Matsuki, J. Chem. Soc. Jpn, 1966, 87, 18b) (400mg) was heated under reflux with $SOCl_2$ (0.7ml) in dry toluene (15ml) for 30 minutes. The toluene was removed *in vacuo* and the residue dried under high vacuum.

1-Piperidineethanol (290mg) was dissolved in dry THF (5ml) and $^nBuLi$ (1.4ml of 1.6M Sol$^n$ in hexane) was added. The mixture was stirred at room temperature for 15 minutes then a solution of the acid chloride from above in dry THF (10ml) was added. The reaction mixture was stirred at room temperature for 2hrs then the solvent was removed *in vacuo*. The residue was partitioned between $H_2O$ and EtOAc and the EtOAc layer removed wased several times with $H_2O$, dried ($MgSO_4$) and concentrated to give a pale yellow oil. This was purified by column chromatography on $SiO_2$ using EtOAc as eluant. The product was isolated as a pale yellow oil and converted to the hydrochloride salt, 30mg mp 192-4°C.

$^1H$ NMR (250MHz) (DMSO) (free base)

δ :9.70(s,1H), 8.5(dd,1H), 8.12(dd,1H), 7.5(dt,2H), 4.4(t,2H), 2.68(t,2H), 3.28-2.49(m,4H), 1.30-1.55(m,6H).

**Example 19**

**(1-Butyl-3-pyrrolidinyl)methyl-4-amino-5-chloro-2-methoxybenzoate hydrochloride** (E19)

To a slurry of 4-amino-5-chloro-2-methoxy benzoic acid (1.00g) in acetonitrile (25 ml) was added bis carbonyl diimidazole (820 mg). The reaction mixture was stirred at ambient temperature for 2h. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane and washed with water. The organic phase was dried and filtered and concentrated *in vacuo*. Crystallisation from hexane/dichloromethane afforded the intermediate imidazolide as a beige solid (983 mg).

To a solution of 1-butyl-3-hydroxymethylpyrrolidine (D1) (485 mg) in dry (THF (20 ml) was added $^{n}$Buli (1.6M in hexane, 1.92 ml) at 0°C under a nitrogen atmosphere. Stirring was continued at ambient temperature for 30 min. The imidazolide (776 mg) in THF (20 ml) was added to the reaction mixture and stirring continued for 20h. Water (1ml) was added and the solvent concentrated *in vacuo*. The residue was partitioned between chloroform and water. The organic phase was dried ($NaSO_4$) filtered and concentrated *in vacuo* to afford crude product. Flash chromatography on silica using chloroform and ethanol gave (1-butyl-3-pyrrolidinyl)methyl-4-amino-5-chloro-2-methoxy benzoate, which was treated with ethereal HCl to afford the title compound (154 mg).

mp 181-184°C.

$^{1}$H NMR ($CD_3OD$) 400 MHz δ: 7.69 (1H, s), 6.47 (1H, s), 4.15-4.32 (4H, m), 3.81 (s, 3H), 3.50-3.59 (1H, m), 3.34-3.41 (2H, m), 3.11-3.16 (3H, m), 2.74-2.83 (1H, m), 2.23-2.34 (1H, m), 1.88-1.99 (1H, m), 1.66-1.75 (2H, m), 1.38-1.48 (2H, m), 0.98 (3H, t)

$MH^+$ 341 ($Cl^+$).

**Example 20**

**(1-Butyl-3-pyrrolidinylmethyl)-1H-indole-3-carboxylate hydrochloride** (E20)

To a slurry of indole-3-carboxylic acid (1.00g) in dichloromethane (20 ml) was added oxalyl chloride (1.1 ml) and N,N'dimethyl formamide (2 drops). The reaction mixture was stirred at ambient temperature for 2h. The solvent was evaporated under reduced pressure to afford crude indole-3 carbonyl chloride (960 mg).

To a solution of 1-butyl-3-hydroxymethylpyrrolidine (D1) (500 mg) in dry THF (20 ml) was added Buli (1.6M in hexanes, 1.99 ml) at 0°C under a nitrogen atmosphere. Stirring was continued at ambient temperature for 30 min. Indole-3-carbonylchloride (571 mg) in dry THF (10 ml) was added

to the reaction mixture and stirring continued for 20h. Water (1 ml) was added to the reaction mixture and the solvent concentrated *in vacuo*. The residue was partitioned between chloroform and water. The organic phase was dried ($NaSO_4$), filtered and concentrated *in vacuo* to afford crude product. Flash chromatography on silica using chloroform and ethanol gave (1-butyl-3-pyrrolidinylmethyl)-1H-indole-3-carboxylate which was treated with ethereal HCl to afford title compound.

m.p 59-62°C

$^1H$ NMR ($CD_3OD$) 270 MHz δ: 7.98-8.05 (m, 2H), 7.41-7.48 (m, 1H), 7.15-7.26 (m, 2H), 4.28-4.47 (m, 2H), 3.51-3.93 (m, 2H), 3.42-3.56 (m, 1H), 2.81-3.25 (m, 4H), 2.19-2.47 (m, 1H), 1.82-2.16 (m, 1H), 1.60-1.80 (m, 2H), 1.34-1.50 (m, 2H), 0.94-1.02 (m, 3H).

$M^+$ 300

**Example 21**

**(1-Pentyl-3-pyrrolidinyl)ethyl 4-amino-5-chloro-2-methoxybenzoate hydrochloride** (E21)

Following the procedure outlined in Example 19, 3-hydroxymethyl-1-pentyl pyrrolidine (D2) (500 mg) gave the title compound (158 mg).

$^1H$ NMR ($d_6$-DMSO) 270 MHz δ: 7.58 (s, 1H), 6.47 (s, 1H), 4.05-4.22 (m, 2H), 3.74 (s, 3H), 3.58-3.70 (m, 1H), 3.36-3.57 (m, 1H), 3.21 (t, 2H), 2.87-3.12 (m, 3H), 2.68-2.84 (q, 1H), 2.28-2.45 (m, 1H), 2.03-2.27 (m, 1H), 1.51-1.91 (m, 5H), 1.18-1.37 (m, 4H), 0.87 (t, 3H).

$M^+$ 368 (Free base)

**Example 22**

**(1-Pentyl-3-pyrrolidinyl)ethyl-1H-indole-3-carboxylate hydrochloride (E22)**

The title compound was prepared in a similar manner to the compound of Example 20.

mp 48-51°C

$^1$H NMR ($d_6$-DMSO) 270 MHz δ: 12.05 (bs, 1H), 8.08 (d, 1H), 7.96-8.03 (m, 1H), 7.45-7.52 (m, 1H), 7.14-7.22 (m, 2H), 4.20-4.33 (m, 2H), 3.42-3.72 (m, 3H), 3.23 (t, 1H), 2.90-3.15 (m, 2H), 2.73 (q, 1H), 2.35-2.82 (m, 1H), 2.06-2.30 (m, 1H), 1.49-1.98 (m, 4H), 1.29-1.47 (m, 4H), 0.88 (t, 3H).

$M^+$ 328 (Free base)

**Example 23**

**(Hexahydro-1-butyl-3-azepinylmethyl)-4-amino-5-chloro-2-methoxy benzoate (E23)**

Following the procedure outlined in Example 19, reaction of hexahydro 1-butyl-3-hydroxymethyl azepine (D3) (500 mg) gave the title compound, as a free base, (318 mg).

mp 72-75°C

$^1$H NMR ($CDCl_3$) 250 MHz δ: 7.82 (s, 1H), 6.29 (s, 1H), 4.50 (bs, 2H), 3.96-4.18 (m, 2H), 3.84 (s, 3H), 2.83 (dd, 1H), 2.61-2.75 (m, 2H), 2.43-2.60 (m, 3H), 2.05-2.20 (m, 1H), 1.21-1.86 (m, 10H), 0.89 (t, 3H).

**Example 24**

**(Hexahydro-1-butyl-3-azepinylmethyl)-1H-indole-3-carboxylate hydrochloride (E24)**

Following the procedure outlined in Example 20, reaction of hexahydro-1-butyl 3-hydroxymethyl azepine (D3) (500 mg) gave the title compound (155 mg).

mp 75-78°C

$^1$H NMR ($CDCl_3$) 250 MHz Free base

δ: 9.45 (m, 1H), 8.14-8.22 (m, 1H), 7.95 (d, 1H), 7.40-7.48 (m, 1H), 7.22-7.31 (m, 2H), 4.10-4.28 (m, 2H), 3.00 (dd, 1H), 2.51-2.89 (m, 5H), 2.23-2.48 (m, 1H), 1.40-1.94 (m, 8H), 1.18-1.33 (m, 2H), 0.82 (t, 3H).

$MH^+$ 329

**Example 25**

**4-Amino-5-Chloro-2-methoxy-(1-butyl-3-piperidyl)ethyl-benzoate (E25)**

Following the procedure outlined in Example 19, reaction of 1-butyl-3-piperidyl ethanol (D4) (1g) gave the title compound as a free base (1.41g).

mp 102-104°C

$^1$H NMR ($CDCl_3$) 250 MHz δ: 7.80 (s, 1H), 6.28 (s, 1H), 4.45 (s, 2H), 4.27 (t, 2H), 3.84 (s, 3H), 2.81-2.96 (m, 2H), 2.25-2.33 (m, 2H), 1.40-1.90 (m, 11H), 1.22-1.48 (m, 2H), 0.92 (t, 3H).

$M^+$ 368

**Example 26**

**(1-Butyl-3-piperidylethyl)-1H-indole-3-carboxylate hydrochloride (E26)**

Following the procedure outlined in Example 21, reaction of 1-butyl-3-piperidyl ethanol (D4) (500 mg) gave the title compound (205 mg).

$^1$H NMR ($CDCl_3$) 250 MHz Free base

δ: 10.02 (s, 1H), 8.13-8.20 (m, 1H), 7.79-7.81 (m, 1H), 7.32-7.44 (m, 1H), 7.19-7.30 (m, 2H), 4.30-4.47 (m, 2H), 2.92-3.08 (m, 2H), 2.31-2.42 (m, 2H), 1.44-1.98 (m, 10H), 1.21-1.35 (m, 2H), 0.83-1.06 (m, 4H).

$M^+$ 328

**Example 27**

**4-Amino-5-chloro-2-methoxy-(1-butyl-2-piperidylethyl)-benzoate (E27)**

Following the procedure outlined in Example 19, reaction of 1-butyl 2-piperidyl ethanol (D5) (750 mg) gave the title compound (650 mg).

mp 75-77°C

$^1$H NMR ($CDCl_3$) 250 MHz δ: 7.81 (s, 1H), 6.29 (s, 1H), 4.48 (s, 2H), 4.19-4.35 (m, 2H), 3.82 (s, 3H), 2.77-2.88 (m, 1H), 2.22-2.70 (m, 4H), 1.99-2.13 (m, 1H), 1.21-1.86 (m, 11H), 0.90 (t, 3H).

$M^+$ 368

**Example 28**

**4-Amino-5-chloro-2-methoxy-(1-butyl 3-piperidylmethyl)- benzoate hydrochloride (E28)**

Following the procedure outlined in Example 19, 1-butyl-3-piperidyl methanol (D6) (500 mg) gave title compound (100 mg).

mp 218-221°C

$^1$H NMR ($CDCl_3$) 250 MHz Free base

δ: 7.81 (s, 1H), 6.27 (s, 1H), 4.46 (s, 2H), 4.00-4.19 (m, 2H), 3.84 (s, 3H), 2.84-3.06 (m, 2H), 2.29-2.38 (m, 2H), 2.01-2.18 (m, 1H), 1.22-1.98 (m, 11H), 0.91 (t, 3H).

$M^+$ 354

**Example 29**

**(1-Butyl-3-piperidylmethyl) 1H-indole-3-carboxylate hydrochloride (E29)**

Following the procedure outlined in Example 20, 1-butyl 3-piperidyl methanol (D6) (500 mg) gave pure title compound (36 mg).

$^1$H NMR ($CDCl_3$) 250 MHz - Free base

δ: 9.96 (s, 1H), 8.17-8.21 (m, 1H), 7.90-7.95 (m, 1H), 7.36-7.44 (m, 1H), 7.21-7.29 (m, 2H), 4.19 (d, 2H), 3.12-3.22 (m, 1H), 2.95-3.04 (m, 1H), 2.31-2.45 (m, 2H), 2.10-2.30 (m, 1H), 1.42-2.06 (m, 6H), 1.03-1.40 (m, 4H), 0.90 (t, 3H).

$MH^+$ 315

**Example 30**

**4-Amino-5-chloro-2-methoxy-(1-butyl-4-piperidyl)benzoate (E30)**

Following the procedure outlined in Example 19, 1-butyl 4-piperidinol (D7) (500 mg) gave the title compound (150 mg).

mp 83-85°C

$^1$H NMR ($CDCl_3$) 250 MHz δ: 7.80 (s, 1H), 6.28 (s, 1H), 4.94-5.05 (m, 1H), 4.47 (s, 2H), 3.83 (s, 3H), 2.66-2.81 (m, 2H), 2.29-2.45 (m, 4H), 1.93-2.08 (m, 2H), 1.76-1.90 (m, 2H), 1.43-1.58 (m, 2H), 1.23-1.41 (m, 2H), 0.93 (t, 3H).

$M^+$ 340

**Example 31**

**4-Amino-5-chloro-2-methoxy-(1-butyl-1,2,5,6-tetrahydro-pyridylmethyl)benzoate (E31)**

Following the procedure outlined in Example 19, 1-butyl (1,2,5,6) tetrahydropiperidyl-4-methanol (D7) (300 mg) gave pure title compound (220 mg).

mp 75-77°C

$^1$H NMR ($CDCl_3$) 250 MHz δ: 7.83 (s, 1H), 6.28 (s, 1H), 5.76 (s, 1H), 4.63 (s, 2H), 4.48 (s, 2H), 3.81 (s, 3H), 3.00 (s, 2H), 2.61 (t, 2H), 2.36-2.56 (m, 2H), 2.25 (m, 2H), 1.46-2.09 (m, 2H), 1.28-1.41 (m, 2H), 0.93 (t, 3H).

$MH^+$ 353

**Example 32**

**(1-Butyl-4-piperidyl)methyl-l-ethyl-1H-indole-3-carboxylate (E32)**

A suspension of 1-ethyl indole-3-carboxylic acid (500 mg) in dichloromethane (50 ml) was treated with oxalyl chloride (0.635g, 0.005 mole) and two drops of dimethylformamide. The mixture was stirred at room temperature for 1½ hours then the solvent was removed *in vacuo* to leave the acid chloride.

A solution of 1-butyl-4-piperidinemethanol (513 mg, 0.003 mole) in dry THF (10 ml) under an atmosphere of nitrogen, was cooled in an ice bath.

n-Butyllithium (1.88 ml of 1.6M solution in hexane) was added dropwise and the resulting solution stirred at 0°C for 15 minutes.

The acid chloride was dissolved in dry THF (20 ml) and the solution added dropwise to the solution of the lithium alkoxide at 0°C.

The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The chloroform was separated, washed several times with water, dried and concentrated to give a pale brown gum which was converted to the hydrochloride salt, mp 158-9°C.

$^1$H NMR (250 MHz) ($CDCl_3$) (free base)

δ: 8.10-8.19 (m, 1H), 7.88 (s, 1H), 7.2-7.38 (m, 3H), 4.20 (m, 4H), 2.92-3.03 (bd, 2H), 2.28-2.40 (m, 2H), 1.20-2.0 (m, 14H), 0.90 (t, 3H).

**Examples 33 and 34**

The following compounds were prepared from the corresponding indole carboxylic acid by the method described for Example 32.

**(1-Butyl-4-piperidyl)methyl-1-methyl-1H-indole-3-carboxylate (E33)**

mp 187-8°C (hydrochloride salt)

$^1$H NMR (250 MHz) ($CDCl_3$) (free base)

δ: 8.10-8.19 (m, 1H), 7.88 (s, 1H), 7.2-7.38 (m, 3H), 4.20 (d, 2H), 3.82 (s, 3H), 2.82-2.98 (bd, 2H), 2.28-2.39 (m, 2H), 1.20-2.18 (m, 11H), 0.90 (t, 3H).

**(1-Cyclohexylmethyl-4-piperidyl)methyl-1-methyl-1H-indole-3-carboxylate (E34)**

mp 164-5°C (hydrochloride salt)

$^1$H NMR (250 MHz) ($CDCl_3$) (free base)

δ: 8.10-8.19 (m, 1H), 7.80 (s, 1H), 7.22-7.4 (m, 3H), 4.20 (d, 2H), 3.82 (s, 3H), 2.86-2.96 (bd, 2H), 2.12 (d, 2H), 0.80-1.98 (m, 18H).

**Example 35**

**(1-Butyl-3-azetidinylmethyl)-4-amino-5-chloro-2-methoxybenzoate (E35)**

Following the procedures outlined above, 1-butyl-3-hydroxymethyl azetidine (D9) (500mg) gave the title compound (240mg). $M^+$ 326

$^1$H NMR 250MHz, $CDCl_3$, δ:7.83 (s,1H), 6.28 (s,1H), 4.50 (bs,2H), 4.33 (d,2H), 3.84 (s,3H), 3.38-3.49 (m,2H), 2.81-3.00 (m,3H), 2.38-2.45 (m,2H), 1.26-1.37 (m,4H), 0.85-0.94 (m,3H)

**Example 36**

**(N-Butylpiperid-4-ylmethyl)-2-methylindole-3-carboxylate (E36)**

Following the procedure outlined in Example 6 (except that methyllithium used in place of n-butyllithium), 2-methylindole-3-carboxylic acid (D1) (950mg) was converted to the title compound (134mg, 8%) mp 128-130°C

$^1$H NMR ($CHCl_3$) 200MHz

δ: 8.1-8.0 (m, 1H), 7.38-6.9 (m, 4H), 4.22 (d, 2H), 3.05 (brd, 2H), 2.75 (s, 3H), 2.5-2.25 (m, 2H), 2.15-1.70 (m, 4H), 1.70-1.15 (m, 7H), 0.92 (t, 3H)

**Example 37**

**(N-Butylpiperid-4-ylmethyl)-2-chloro-l-methylindole-3-carboxylate hydrochloride (E37)**

Following the procedure outlined in GB 2125398A, Example A5, N-Butylpiperid-4-ylmethyl-l-methyl)indole-3-carboxylate (E33) (300mg) was converted to the title compound (65mg, 15%) mp 238-40°C

$^1$H NMR ($CDCl_3$) 200MHz (free base)

δ: 8.18-8.05 (m, 1H), 7.33-7.20 (m, 3H), 4.24 (d, 2H), 3.77 (s, 3H), 3.05 (brd, 2H), 2.49-2.3 (m, 2H), 2.12-1.7 (m, 5H), 1.65-1.15 (m, 6H), 0.92 (t, 3H)

**Example 38**

**(N-Butylpiperid-4-ylmethyl)-2-methoxyindole-3-carboxylate hydrochloride (E38)**

Following the procedure outlined in GB 2125398A Example A5, (N-butylpiperid-4-ylmethyl)indole-3-carboxylate (E6) (0.25g) was converted to the title compound (108mg, 36%) mp 168-170°C.

$^1$H NMR ($CDCl_3$) 250MHz (free base)

δ: 7.95 (d, 1H), 7.3-7.05 (m, 3H), 4.20 (d, 2H), 4.07 (s, 3H), 3.07 (brd, 2H), 2.49-2.36 (m, 2H), 2.09 (br t, 2H), 1.99-1.75 (m, 3H), 1.7-1.2 (m, 6H), 0.91 (t, 3H)

**Example 39**

**(N-Butylpiperid-4-ylmethyl)indole-3-carboxamide (E39)**

To a stirring solution of indole-3-carboxylic acid (1g) in dichloromethane (20ml) at 0°C under nitrogen was added oxalyl chloride (0.81 ml) and dry dimethylformamide (3 drops). After 3 hours, the solvents were evaporated under reduced pressure. A portion of the residual acid chloride (420mg) was dissolved in dichloromethane (12ml) and added dropwise to a solution of N-butylpiperid-4-ylmethylamine (400mg) in dichloromethane 12ml) followed by triethylamine (0.36ml). After stirring at ambient temperature overnight, the reaction mixture was washed with saturated $NaHCO_3$ and the organic phase was dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the residue recrystallised from ethylacetate to give the title compound (467mg, 64°C).

$^1$H NMR ($CDCl_3$) 250MHz

δ: 9.29 (br s, 1H), 8.05-7.9 (m, 1H), 7.81 (d, 1H), 7.55-7.4 (m, 1H), 7.39-7.2 (m, 2H), 6.28 (br s, 1H), 3.39 (t, 2H), 3.0 (br d, 2H), 2.45-2.25 (m, 2H), 2.1-

1.1 (m, 11H), 0.9 (t, 3H)

**Example 40**

**(N-Butylpiperid-4-ylmethyl)-2-methoxyindole-3-carboxamide hydrochloride (E40)**

Following the procedure outlined in GB 2125398A, Example A5, (N-Butylpiperid-4-ylmethyl)indole-3-carboxamide (E39) (220mg) was convered to the title compound (230mg, 86%). Mp 138-144°C

$^1$H NMR ($CDCl_3$) 250MHz (free base)

δ 9.85 (br s, 1H), 8.25 (d, 1H), 7.4-7.0 (m, 3H), 6.78 (t, 1H), 4.18 (s, 3H), 3.35 (t, 2H), 2.98 (br d, 2H), 2.45-2.25 (m, 2H), 1.95 (br t, 2H), 1.82-1.2 (m, 9H), 0.91 (t, 3H)

**Example 41**

**1-Piperidylethyl-2-methylindole-3-carboxylate hydrochloride (E41)**

Following the procedure outlined in Example 36, 2-methylindole-3-carboxylic acid (490 mg) was converted to the title compound (76mg) mp 147-9°C.

$^1$H NMR ($CDCl_3$) 200 MHz

δ: 8.65(br s,1H), 8.15-8.00(m,1H), 7.35-7.00(m,3H), 4.49(t,2H), 2.82(t,2H), 2.68(s,3H), 2.6-2.45(m,4H), 1.7-1.35(m,6H).

**Example 42**

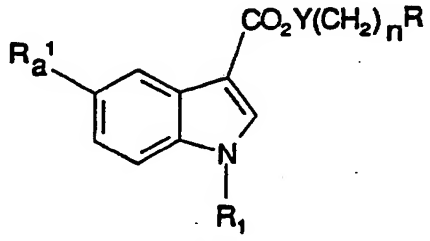
**4-Amino-3,5-dichloro-2-methoxy-(1-butyl-4-piperidyl)methyl benzoate (E42)**

The title compound was prepared from 4-amino-3,5-dichloro-2-methoxybenzoic acid and 1-butyl-4-piperidylmethanol by the method described in Example 2, except that MeLi was used in place of $^{n}$BuLi. The product was isolated as the hydrochloride salt.

mp 190-191°C

$^{1}$H NMR (200MHz) $CDCl_3$ (free base) δ: 7.72(s,1H), 4.9(bs,2H), 4.12(d,2H), 3.85(s,3H), 2.85-3.0(bd,2H), 2.2-2.34(m,2H), 1.2-2.00(m,11H), 0.90(t,3H).

Further compounds of potential use in the invention which were prepared are as follows:




| $R_a^1$ | $R_1$ | Y | n | R | m.p. |
|---|---|---|---|---|---|
| H | Et | O | 2 | 1-piperidyl | 175-177°C |
| H | $^n$Pr | O | 2 | 1-piperidyl | 198-199°C |
| H | $^n$Bu | O | 2 | 1-piperidyl | 202-204°C |
| MeO | H | O | 2 | 1-piperidyl | 142-144°C |
| Cl | H | O | 2 | 1-piperidyl | 153.5-154.5°C |
| H | H | O | 2 | NHBz | 233-235°C |
| H | H | O | 4 | $N(CH_3)_2$ | 153-4°C |
| H | H | O | 2 | $N(CH_3)_2$ | 108-9°C |
| H | H | O | 3 | $N(CH_3)_2$ | 208-210°C |
| H | H | O | 2 | $N(Et)_2$ | 156-7°C |
| H | H | NH | 2 | $N(CH_3)_2$ | 194-5°C |
| H | H | NH | 2 | $N(Et)_2$ | 97-98°C |
| H | Bz | O | 2 | $N(CH_3)_2$ | 165-166°C |
| H | Bz | O | 4 | $N(CH_3)_2$ | 138-9°C |

## 5-$HT_4$ RECEPTOR ANTAGONIST ACTIVITY

### 1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% $CO_2$ in $O_2$ and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin $10^{-7}$M and granisetron $10^{-6}$M to block effects at 5-$HT_1$, 5-$HT_2$ and 5-$HT_3$ receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum($10^{-9}$M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-$HT_4$ receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, $pIC_{50}$ values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-$HT_4$ receptor antagonist.

Compounds were generally active in the range of concentrations of the order of $pIC_{50}$=6 or more, E4 and E7 showing particularly good activity.

### 2) Piglet Atria

Compounds were tested in the piglet spontaneous beating screen (Naunyn-Schmiedeberg's Arch. Pharmacol 342, 619-622). $pK_B$ ($-\log_{10} K_B$) value for the compounds were generally of the order of 6 or more, E6 and E16 showing particularly good activity.

3) **Rat oesophagus**

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% $O_2$/5% $CO_2$) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

4) **5-HT-induced motility in dog gastric pouch**

Compounds are tested for inhibition in the *in vivo* method described in "Stimulation of canine motility by BRL 24924, a new gastric prokinetic agent", Bermudez *et al*, J. Gastrointestinal Motility, 1990, 2(4), 281-286.

## Claims

1. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof;

X-CO-Y-Z (I)

wherein X, Y and Z are as defined in the specification, in the manufacture of a medicament for use as a 5-$HT_4$ receptor antagonist.

2. The use according to claim 1 for use as a 5-$HT_4$ antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

3. The use according to claim 2 for use in the treatment of IBS.

4. The use according to claim 2 for use in the treatment of gastro-oesophagal reflux disease and dyspepsia.

5. The use according to claim 2 for use in the treatment of atrial arrhythmias and stroke.

6. The use according to claim 2 for use in the treatment of anxiety.

7. The use according to claim 2 for use in the treatment of migraine.

8. The use of 2-piperidinoethyl 1H-indole-3-carboxylate or any one of the compounds of the Examples, E1 to E42, in the manufacture of a medicament for use as a 5-$HT_4$ receptor antagonist.

9. A compound selected from the compounds of Examples 1 to 42, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to claim 9, and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01519

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)°

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/445 A 61 K 31/395 A 61 K 31/47
A 61 K 31/40 A 61 K 31/55 A 61 K 31/415 A 61 K 31/38

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 K 31/00 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0429984 (NISSHIN FLOUR MILLING CO.) 5 June 1991, see the entire document (cited in the application) --- | 8 |
| X | Naunyn-Schmiedeberg's Arch. Pharmacol., Abstracts of the 32nd Spring Meeting, Mainz, 12-15 March 1991, vol. 343, suppl., K.H. BUCHHEIT et al.: "SDZ 205-557, a new antagonist for 5-HT4 receptors in the isolated guinea pig ileum", page R 101, abstract no. 402, see the entire abstract (cited in the application) --- -/- | 8 |

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 12-11-1992 | 30. 12. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Mme Dagmar FRANK |

Form PCT/ISA/210 (second sheet) (January 1985)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB92/01519

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
THE SUBJECT MATTER OF CLAIMS 1-10 VIOLATES THE REQUIREMENTS OF ART.6 AND RULE 6.2 PCT.ONLY CLAIM 8 WAS FOUND TO BE PARTIALLY SEARCHABLE. THE ATTENTI ON OF THE APPLICANT IS DRAWN TO THE FACT THAT UPON FILING OF AMENDED CLAIM S, UNITY OF INVENTION HAS TO BE REASSESSED, AND THIS COULD RESULT IN A POSSIBLE REQUEST FOR PAYMENT OF ADDITIONAL SEARCH FEES.

3. ☒ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201519 SA 63421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/12/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A- 0429984 | 05-06-91 | JP-A- | 3223250 | 02-10-91 |
| | | US-A- | 5124324 | 23-06-92 |
| GB-A- 2125398 | 07-03-84 | AT-B- | 391136 | 27-08-90 |
| | | AU-B- | 570002 | 03-03-88 |
| | | AU-A- | 1628683 | 05-01-84 |
| | | AU-B- | 603399 | 15-11-90 |
| | | AU-A- | 8243487 | 28-04-88 |
| | | CH-A- | 669792 | 14-04-89 |
| | | CH-A- | 669954 | 28-04-89 |
| | | WO-A- | 8400166 | 19-01-84 |
| | | DE-A,C | 3322574 | 29-12-83 |
| | | DE-A,C | 3348331 | 31-08-89 |
| | | DE-A,C | 3348332 | 07-09-89 |
| | | DE-A,C | 3348333 | 24-08-89 |
| | | DE-A,C | 3348334 | 31-08-89 |
| | | FR-A,B | 2531083 | 03-02-84 |
| | | GB-A,B | 2166726 | 14-05-86 |
| | | GB-A,B | 2166727 | 14-05-86 |
| | | GB-A,B | 2166728 | 14-05-86 |
| | | NL-A- | 8302253 | 16-01-84 |
| | | SE-B- | 463210 | 22-10-90 |
| | | SE-A- | 8303651 | 30-12-83 |
| | | US-A- | 4803199 | 07-02-89 |
| | | US-A- | 4910207 | 20-03-90 |
| | | US-A- | 5017582 | 21-05-91 |
| | | BE-A- | 897117 | 23-12-83 |
| | | CA-A,C | 1257870 | 25-07-89 |
| | | JP-A- | 59067284 | 16-04-84 |
| | | JP-A- | 59036675 | 28-02-84 |
| | | US-A- | 4789673 | 06-12-88 |
| EP-A- 0189002 | 30-07-86 | DE-A- | 3446484 | 03-07-86 |
| | | DE-A- | 3531281 | 12-03-87 |
| | | DE-A- | 3531282 | 12-03-87 |
| | | AU-B- | 595172 | 29-03-90 |
| | | AU-A- | 5139685 | 31-07-86 |
| | | JP-A- | 2237920 | 20-09-90 |
| | | JP-A- | 61152628 | 11-07-86 |

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201519 SA 63421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 08/12/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP-A- 0200444 | 05-11-86 | AU-B- 594670 | 15-03-90 |
| | | AU-A- 5657986 | 06-11-86 |
| | | CA-A- 1296004 | 18-02-92 |
| | | EP-A- 0498466 | 12-08-92 |
| | | JP-A- 61275276 | 05-12-86 |
| | | US-A- 4937247 | 26-06-90 |
| | | US-A- 4886808 | 12-12-89 |
| | | US-A- 5034398 | 23-07-91 |
| | | EP-A- 0223385 | 27-05-87 |

REVISED VERSION *

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/445, 31/395, 31/47
A61K 31/40, 31/55, 31/415
A61K 31/38

A1

(11) International Publication Number: WO 93/03725

(43) International Publication Date: 4 March 1993 (04.03.93)

(21) International Application Number: PCT/GB92/01519

(22) International Filing Date: 18 August 1992 (18.08.92)

(30) Priority data:

| | | |
|---|---|---|
| 9117943.2 | 20 August 1991 (20.08.91) | GB |
| 9119692.3 | 14 September 1991 (14.09.91) | GB |
| 9201414.1 | 23 January 1992 (23.01.92) | GB |
| 9203977.5 | 25 February 1992 (25.02.92) | GB |
| 9208321.1 | 15 April 1992 (15.04.92) | GB |


(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : KING, Francis, David [GB/GB]; GASTER, Laramie, Mary [GB/GB]; JOINER, Graham, Francis [GB/GB]; RAHMAN, Shirley, Katherine [GB/GB]; SANGER, Gareth, John [GB/GB]; WARDLE, Kay, Alison [GB/GB]; BAXTER, Gordon, Smith [GB/GB]; KENNETT, Guy, Anthony [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). YOUNG, Rodney, Christopher [GB/GB]; VIMAL, Mythily [LK/GB]; KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

**Published**
*With a revised version of the international search report.*

(88) Date of publication of the revised version of the international search report:
15 April 1993 (15.04.93)

(54) Title: 5-HT4 RECEPTOR ANTAGONISTS

(57) Abstract

Compounds of formula (I): X-CO-Y-Z wherein the variable groups are as defined in the specification, of use in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | |
|---|---|
| AT | Austria |
| AU | Australia |
| BB | Barbados |
| BE | Belgium |
| BF | Burkina Faso |
| BG | Bulgaria |
| BJ | Benin |
| BR | Brazil |
| CA | Canada |
| CF | Central African Republic |
| CG | Congo |
| CH | Switzerland |
| CI | Côte d'Ivoire |
| CM | Cameroon |
| CS | Czechoslovakia |
| CZ | Czech Republic |
| DE | Germany |
| DK | Denmark |
| ES | Spain |
| FI | Finland |
| FR | France |
| GA | Gabon |
| GB | United Kingdom |
| GN | Guinea |
| GR | Greece |
| HU | Hungary |
| IE | Ireland |
| IT | Italy |
| JP | Japan |
| KP | Democratic People's Republic of Korea |
| KR | Republic of Korea |
| LI | Liechtenstein |
| LK | Sri Lanka |
| LU | Luxembourg |
| MC | Monaco |
| MG | Madagascar |
| ML | Mali |
| MN | Mongolia |
| MR | Mauritania |
| MW | Malawi |
| NL | Netherlands |
| NO | Norway |
| NZ | New Zealand |
| PL | Poland |
| PT | Portugal |
| RO | Romania |
| RU | Russian Federation |
| SD | Sudan |
| SE | Sweden |
| SK | Slovak Republic |
| SN | Senegal |
| SU | Soviet Union |
| TD | Chad |
| TG | Togo |
| UA | Ukraine |
| US | United States of America |

**REVISED VERSION**

# INTERNATIONAL SEARCH REPORT

International Appli n No PCT/GB 92/01519

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/445 A 61 K 31/395 A 61 K 31/47
A 61 K 31/40 A 61 K 31/55 A 61 K 31/415 A 61 K 31/38

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 K 31/00 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0429984 (NISSHIN FLOUR MILLING CO.) 5 June 1991, see the entire document (cited in the application) --- | 8 |
| X | Naunyn-Schmiedeberg's Arch. Pharmacol., Abstracts of the 32nd Spring Meeting, Mainz, 12-15 March 1991, vol. 343, suppl., K.H. BUCHHEIT et al.: "SDZ 205-557, a new antagonist for 5-HT4 receptors in the isolated guinea pig ileum", page R 101, abstract no. 402, see the entire abstract (cited in the application) --- -/- | 8 |

[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 12-11-1992 | 30. 12. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Mme Dagmar FRANK |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| Y | European Journal of Pharmacology, vol. 183, no. 4, July 1990, Elsevier Science Publishers B.V., M.A. PETTY et al.: "Anti arrhythmic activity of the 5-HT3 receptor antagonist MDL 73147 in different species", page 1159, see the entire abstract | 8 |
| Y | J. Auton. Pharmacol., vol. 5, no. 2, June 1985, P.R. SAXENA et al.: "Excitatory 5-hydroxytryptamine receptors in the cat urinary bladder are of the M-and 5HT2-type", pages 101-107, see the entire document | 8 |
| Y | GB,A,2125398 (SANDOZ) 7 March 1984, see page 13, lines 34-58 (cited in the application) | 8 |
| X | EP,A,0189002 (SANDOZ) 30 July 1986, see page 19 (cited in the application) | 8 |
| Y | EP,A,0200444 (BEECHAM) 5 November 1986, see page 20, last paragraph (cited in the application) | 8 |
| Y | Naunyn-Schmiedeberg's Arch. Pharmacol., vol. 342, no. 5, November 1990, A.J. KAUMANN: "Piglet sinoatrial 5-HT receptors resemble human atrial 5-HT4-like receptors", pages 619-622, see the entire document (cited in the application) | 8 |
| X | European Journal of Pharmacology, vol. 200, nos. 2-3, 6 August 1991, Elsevier Science Publishers B.V., K.-H. BUCHHEIT et al.: "SDZ 205-557, a selective antagonist at 5-HT4 receptors in the isolated guines pig ileum", pages 373-374, see the entire document | 8 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB92/01519

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
THE SUBJECT MATTER OF CLAIMS 1-10 VIOLATES THE REQUIREMENTS OF ART. 6 AND RULE 6.2 PCT. ONLY CLAIM 8 WAS FOUND TO BE PARTIALLY SEARCHABLE. THE ATTENTI ON OF THE APPLICANT IS DRAWN TO THE FACT THAT UPON FILING OF AMENDED CLAIM S, UNITY OF INVENTION HAS TO BE REASSESSED, AND THIS COULD RESULT IN A POSSIBLE REQUEST FOR PAYMENT OF ADDITIONAL SEARCH FEES.

3. ☒ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

REVISED VERSION *

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/445, 31/395, 31/47
A61K 31/40, 31/55, 31/415
A61K 31/38

A3
A1

(11) International Publication Number: WO 93/03725

(43) International Publication Date: 4 March 1993 (04.03.93)

(21) International Application Number: PCT/GB92/01519

(22) International Filing Date: 18 August 1992 (18.08.92)

(30) Priority data:

| | | |
|---|---|---|
| 9117943.2 | 20 August 1991 (20.08.91) | GB |
| 9119692.3 | 14 September 1991 (14.09.91) | GB |
| 9201414.1 | 23 January 1992 (23.01.92) | GB |
| 9203977.5 | 25 February 1992 (25.02.92) | GB |
| 9208321.1 | 15 April 1992 (15.04.92) | GB |

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : KING, Francis, David [GB/GB]; GASTER, Laramie, Mary [GB/GB]; JOINER, Graham, Francis [GB/GB]; RAHMAN, Shirley, Katherine [GB/GB]; SANGER, Gareth, John [GB/GB]; WARDLE, Kay, Alison [GB/GB]; BAXTER, Gordon, Smith [GB/GB]; KENNETT, Guy, Anthony [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). YOUNG, Rodney, Christopher [GB/GB]; VIMAL, Mythily [LK/GB]; KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

**Published**
*With a revised version of the international search report.*

**(88) Date of publication of the revised version of the international search report:**
15 April 1993 (15.04.93)

(54) Title: 5-HT4 RECEPTOR ANTAGONISTS

(57) Abstract

Compounds of formula (I): X-CO-Y-Z wherein the variable groups are as defined in the specification, of use in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | |
|---|---|
| AT | Austria |
| AU | Australia |
| BB | Barbados |
| BE | Belgium |
| BF | Burkina Faso |
| BG | Bulgaria |
| BJ | Benin |
| BR | Brazil |
| CA | Canada |
| CF | Central African Republic |
| CG | Congo |
| CH | Switzerland |
| CI | Côte d'Ivoire |
| CM | Cameroon |
| CS | Czechoslovakia |
| CZ | Czech Republic |
| DE | Germany |
| DK | Denmark |
| ES | Spain |
| FI | Finland |
| FR | France |
| GA | Gabon |
| GB | United Kingdom |
| GN | Guinea |
| GR | Greece |
| HU | Hungary |
| IE | Ireland |
| IT | Italy |
| JP | Japan |
| KP | Democratic People's Republic of Korea |
| KR | Republic of Korea |
| LI | Liechtenstein |
| LK | Sri Lanka |
| LU | Luxembourg |
| MC | Monaco |
| MG | Madagascar |
| ML | Mali |
| MN | Mongolia |
| MR | Mauritania |
| MW | Malawi |
| NL | Netherlands |
| NO | Norway |
| NZ | New Zealand |
| PL | Poland |
| PT | Portugal |
| RO | Romania |
| RU | Russian Federation |
| SD | Sudan |
| SE | Sweden |
| SK | Slovak Republic |
| SN | Senegal |
| SU | Soviet Union |
| TD | Chad |
| TG | Togo |
| UA | Ukraine |
| US | United States of America |
| VN | Viet Nam |

**REVISED VERSION**

# INTERNATIONAL SEARCH REPORT

International Appli n No PCT/GB 92/01519

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/445 A 61 K 31/395 A 61 K 31/47
A 61 K 31/40 A 61 K 31/55 A 61 K 31/415 A 61 K 31/38

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 K 31/00 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document.[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0429984 (NISSHIN FLOUR MILLING CO.) 5 June 1991, see the entire document (cited in the application) --- | 8 |
| X | Naunyn-Schmiedeberg's Arch. Pharmacol., Abstracts of the 32nd Spring Meeting, Mainz, 12-15 March 1991, vol. 343, suppl., K.H. BUCHHEIT et al.: "SDZ 205-557, a new antagonist for 5-HT4 receptors in the isolated guinea pig ileum", page R 101, abstract no. 402, see the entire abstract (cited in the application) --- -/- | 8 |

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 12-11-1992 | 30. 12. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Mme Dagmar FRANK |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| Y | European Journal of Pharmacology, vol. 183, no. 4, July 1990, Elsevier Science Publishers B.V., M.A. PETTY et al.: "Anti arrhythmic activity of the 5-HT3 receptor antagonist MDL 73147 in different species", page 1159, see the entire abstract | 8 |
| Y | J. Auton. Pharmacol., vol. 5, no. 2, June 1985, P.R. SAXENA et al.: "Excitatory 5-hydroxytryptamine receptors in the cat urinary bladder are of the M-and 5HT2-type", pages 101-107, see the entire document | 8 |
| Y | GB,A,2125398 (SANDOZ) 7 March 1984, see page 13, lines 34-58 (cited in the application) | 8 |
| X | EP,A,0189002 (SANDOZ) 30 July 1986, see page 19 (cited in the application) | 8 |
| Y | EP,A,0200444 (BEECHAM) 5 November 1986, see page 20, last paragraph (cited in the application) | 8 |
| Y | Naunyn-Schmiedeberg's Arch. Pharmacol., vol. 342, no. 5, November 1990, A.J. KAUMANN: "Piglet sinoatrial 5-HT receptors resemble human atrial 5-HT4-like receptors", pages 619-622, see the entire document (cited in the application) | 8 |
| X | European Journal of Pharmacology, vol. 200, nos. 2-3, 6 August 1991, Elsevier Science Publishers B.V., K.-H. BUCHHEIT et al.: "SDZ 205-557, a selective antagonist at 5-HT4 receptors in the isolated guines pig ileum", pages 373-374, see the entire document | 8 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB92/01519

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
THE SUBJECT MATTER OF CLAIMS 1-10 VIOLATES THE REQUIREMENTS OF ART.6 AND RULE 6.2 PCT.ONLY CLAIM 8 WAS FOUND TO BE PARTIALLY SEARCHABLE. THE ATTENTI ON OF THE APPLICANT IS DRAWN TO THE FACT THAT UPON FILING OF AMENDED CLAIM S, UNITY OF INVENTION HAS TO BE REASSESSED, AND THIS COULD RESULT IN A possible request for payment of additional search fees.

3. ☒ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.